SCIENTIFIC DISCUSSION

1 SUMMARY OF THE DOSSIER

Trocoxil, chewable tablets for dogs, contain mavacoxib as the active substance and the triangular shaped tablets are presented in five different strengths (6 mg, 20 mg, 30 mg, 75 mg, 95 mg). They are intended for treatment of pain and inflammation associated with degenerative joint disease in dogs in cases where continuous treatment exceeding one month is indicated. The Applicant for this veterinary medicinal product is Pfizer Ltd, United Kingdom.

The active substance of Trocoxil is mavacoxib, a non-steroidal anti-inflammatory drug (NSAID) of the coxib class (ATCvet Code QM01AH92). Mavacoxib - 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is used in the treatment of chronic pain and inflammation associated with osteoarthritis in dogs. It is a specific inhibitor of the inducible form of cycloxygenase.

The benefits of Trocoxil are its relief of pain and inflammation in dogs with degenerative joint disease. This is a MONTHLY treatment where the initial dose is given in accordance with the posology on the SPC, repeated 14 days later and then monthly dosed for up to a maximum of 7 consecutive doses (6.5 months). The most common side effects are loss of appetite, diarrhea and vomiting which have occasionally been reported.

The approved indication is: "For the treatment of pain and inflammation associated with degenerative joint disease in dogs in cases where continuous treatment exceeding one month is indicated".

The pharmacovigilance system in place complies with the requirements in the guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections for veterinary medicinal products in Volume 9 of the Rules governing medicinal products in the EU.

2. QUALITY ASSESSMENT

Composition

Trocoxil tablets are manufactured from a common blend containing 5% w/w mavacoxib. The full composition of the 6, 20, 30, 75 and 95 mg tablets has been provided. The tablets contain common pharmaceutical excipients that comply with Ph.Eur or in-house standards and also an artificial powdered beef flavour.

Container

Trocoxil chewable tablets are packaged in blisters. Carton boxes each contain one blister. Each blister contains two tablets of 6 mg, 20 mg, 30 mg, 75 mg or 95 mg, respectively. Studies have been performed to establish the compatibility, safety and performance of the proposed packaging.

Clinical Trial Formula(e)

Information was provided on formulations used in clinical studies. The tablets have stayed unaltered throughout development and are the same as those proposed for marketing.

Development Pharmaceutics

Trocoxil has been developed as chewable tablets for once-a-month dosing for dogs. The strengths in focus have been changed during development but the tablets applied for are 6 mg, 20 mg, 30 mg, 75 mg and 95 mg. All strengths are manufactured from a common blend containing 5 % w/w of mavacoxib. Five crystalline forms (I to V) of mavacoxib exist and are distinguished by powder X-ray diffraction. There are two crystalline non-solvated forms and three solvated forms. No hydrates exist. Form I is used for the formulation and is an anhydrous, non-solvated and non-hygroscopic form. The

excipients have been selected for their properties such as: improving palatability, solubiliser, filler, compression aid, disintegrant and lubricant. A variety of excipients have been tried during formulation development, *e.g.* two different particle size compressible sugar, spray dried lactose monohydrate as filler, traditional as well as densified microcrystalline cellulose. Silicified microcrystalline cellulose demonstrated enhanced flowability properties as compared to the other grades of microcrystalline cellulose. The level of artificial flavour was decided on early in development as it proved to offer optimal palatability. Inclusion of sodium laurilsulphate is to increase bioavailability. The magnesium stearate concentration has been optimised considering the balance between powder handling properties and lubrication. Due to the hygroscopic nature of the beef flavour as well as croscarmellose sodium an Al/Al foil blister has been selected as primary packaging. A justification for the classification as chewable tablets has been provided and accepted. Ph.Eur. Friability and Resistance to Crushing procedures are utilised to demonstrate a tablet is masticable.

The tablets are intended for chewing but may also be swallowed whole. Therefore a control for dissolution consistent with that for an immediate release tablet was developed.

Manufacture and scale up throughout development is thoroughly accounted for. Conventional direct compression tablet manufacture has been used throughout development. The process and equipment used during development utilised the same principles as proposed for the commercial process. Parameters considered are the particle size of the drug substance and furthermore those related to the instrumentation and equipment. The robustness of the proposed commercial process has been confirmed through so-called qualification studies. In these studies different process parameters as e.g. blend speed, blend time and screen size has been investigated in combination with each other and also interaction effects been evaluated. No critical steps have been identified.

Method of Manufacture

The manufacturing formula is given for the commercial batch size. A common blend is used for all tablet strengths. Manufacturer of Trocoxil chewable tablets involves sites at Pfizer Lincoln USA for manufacture and testing, Sharp PA USA for packaging, Pfizer Germany for batch release and testing and Pfizer Italia as an alternate site for manufacture, testing, packaging, release and stability testing.

The manufacturing process is well described and a detailed process flow chart provided. The process is a conventional tablet manufacture and comprises blending of drug substance and all excipients apart from magnesium stearate, screening of blend, addition of screened magnesium stearate, final blending, compression and packaging. Tablets are checked for weight, thickness and hardness at regular intervals during compression. Hold time studies of blend storage and bulk tablets were performed.

A validation plan was provided for full scale manufacture at the proposed commercial manufacturing site. Considering the non-critical process it is acceptable that process validation is not performed prior to approval. The applicant will carry out process validation on 3 production scale batches prior to marketing.

Control of Starting Materials

Active Substance

Mavacoxib is not detailed in any pharmacopoeia. The detailed specification including appearance, identification, particle size, assay, tests for heavy metals and water, residue on ignition, residual solvents and impurities for mavacoxib drug substance is presented in the dossier.

Limits for each residual solvent (class 1 and 2) were specified, and residual solvents have been reduced to a practical minimum.

Satisfactory method descriptions are provided for each of the specification methods. Validation data provided confirm the suitability of the methods to control the corresponding parameter to the proposed acceptance criteria. The HPLC method for assay and impurities (related substances) as well as the GC

method for residual solvents are demonstrated to be linear, precise, accurate and robust within the defined ranges. Investigations confirm that the HPLC method can quantify with sufficient precision down to at least 0.10%.

The nomenclature for mavacoxib is included in the dossier along with its structural formula and molecular weight. Mavacoxib is a white to off-white powder. Five crystalline forms (I to V) exist and are distinguished by powder X-ray diffraction. These are two non-solvated forms and three solvated forms. No hydrates exist. Form I is used for the formulation and is an anhydrous, non-solvated and non-hygroscopic form. The form is chemically and physically stable under ambient conditions. Mavacoxib is practically insoluble in water over the range (pH 1.2 to pH 6.8).

The manufacturers of mavacoxib drug substance include Pfizer UK as API manufacturer and suppliers of the starting materials for the synthesis of mavacoxib drug substance are all listed in the dossier. Mavacoxib drug substance is manufactured through a two-step synthesis. No specifications have been developed for the two intermediates during the synthesis. This is acceptable as the first intermediate is a non-stable intermediate not isolated and as no impurities needing immediate purging are formed during step 1A. Also for the second intermediate, (isolated as a damp product or dried product) in step 1B no testing is proposed as there is no re-processing step and potential impurities are controlled during the subsequent step.

The manufacturing process is described as well as a process flow chart provided. Solvents used in the manufacturing process are ethanol, isopropanol and methanol. Mavacoxib drug substance is stored in double polyethylene liners (closed with plastic ties) inside high density polyethylene drums closed with tamper evident closure. A specification for the polyethylene liner is provided as are instructions for visual evaluation of packaging materials.

Specifications are provided for the starting materials together with justifications of the same, method descriptions and summarised method validations. The specifications are discussed in the dossier and rationales based on e.g. batch data and knowledge about purging in the starting materials synthesis or in the synthesis of mavacoxib drug substance. Potential impurities in the starting materials are discussed.

The structure of mavacoxib drug substance has been confirmed by use of elemental analysis and spectroscopic methods as UV, IR, NMR (^{1}H, ^{13}C and ^{19}F) and MS. The crystal structure has been confirmed by use of X-ray diffraction, (powder and single crystal), Differential scanning calorimetry and Thermal analysis. Copies of spectra, diffraction patterns and thermograms are provided together with interpretations. The non-hygroscopic nature of mavacoxib has been confirmed by water sorption studies. Solubility data for mavacoxib in aqueous solutions with different pH are provided. The pKa for mavacoxib is 9.57 (+/- 0.01). It is confirmed that Form I is consistently formed by use of the current manufacturing process and specifically in relation to the drug substance isolation process. Conditions, assuring Form I, are discussed as are also those that could possibly yield Form II.

Data are provided for 12 batches manufactured by the commercial synthetic route. Batch data confirm satisfactory uniformity and compliance with the specification and demonstrate that active substance of the desired quality can be consistently produced.

Three pilot scale drug substance batches were manufactured according to the commercial route and process and stored in the proposed packaging for 24 months at 25°C/60%RH and 30°C/65%RH and for 6 months at 40°C/75%RH. The batches have been tested according to the proposed specification. No significant degradation occurs. There is no increase in levels of impurities, the assay remains constant, the water content does not increase and crystal Form I is confirmed throughout storage. Photostability studies have confirmed that mavacoxib active substance is not light sensitive. The proposed re-test period of 3 years for mavacoxib stored in the intended package was accepted.

Excipients

All excipients apart from compressible sugar, silicified microcrystalline cellulose and artificial powdered beef flavour are controlled according to the corresponding monographs of the European Pharmacopoeia.

Silicified microcrystalline cellulose is a mixture of microcrystalline cellulose (Ph.Eur.) and anhydrous colloidal silica (Ph.Eur.) An in-house monograph is used for the mix. Prosolv® SMCC90 is manufactured via a patented mixture of microcrystalline cellulose and anhydrous colloidal silica. The silification of the microcrystalline cellulose is achieved by addition of anhydrous colloidal silica prior to the drying step during the manufacturing process. Separate monograph testing for microcrystalline cellulose cannot be carried out because of co-processing. Sulphated ash is used to quantify the amount of anhydrous colloidal silica present in the silicified microcrystalline cellulose.

Artificial beef flavour consists of hydrolysed vegetable protein (from soybeans), hydrogenated vegetable oil (from soybeans) and desiccated pork liver powder (from pork livers of swine raised in USA). All three ingredients of the flavour are FDA approved human food ingredients (complying with FDA law and regulations). Gamma Irradiation of the artificial powdered beef flavour, (PC-0125) is carried out on behalf of Pharma Chemie by Steris Isomedix Services, Libertyville, Illinois. The limits established for microbiological purity are sufficient to guarantee the quality of the tablets. Typical spectra were provided.

Satisfactory certificates of analysis are provided for each of the excipients.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Declarations are provided for the excipients in relation to the risk for transmission of spongiform encephalopathies. No materials of animal origin are used during the synthesis of mavacoxib drug substance. Apart for the pork liver in the artificial powdered beef flavour there are no ingredients of animal origin in the tablets. Concerning the beef flavour a declaration from the supplier is provided stating that the flavour is composed of human food grade ingredients. The porcine material is declared to be from swine or pigs of USA origin and all material are stated to come from United States Department of Agriculture (USDA) inspected and approved facilities within the US. A declaration is provided stating that all the components used in the manufacture of Trocoxil comply with Directive 1999/104/EC and the current TSE guideline (EMEA/410/01-Rev. 2).

Control Tests on the Finished Product

Release and shelf-life specifications and details of routine tests for control of Trocoxil finished product including appearance, identity of the active, assay, content uniformity, dissolution, individual and total degradation products and water content were provided. The microbiological control test included in the finished product specifications will comply with the limits established in Category 3A of Ph.Eur. for oral preparations.

Relevant test parameters and methods are included and acceptance criteria are based on batch data as well as on stability data. Ranges of results are presented from batches produced during development and manufactured with the proposed commercial process.

The dissolution method is included in the specification to control product quality. The method parameters have been selected so as to obtain sink conditions for the highest tablet strength *i.e.* to assure that when all drug substance is dissolved the concentration of the solution is equal to or less than a third of the saturation solution of mavacoxib. The dissolution method has been confirmed to discriminate between tablets containing and not containing disintegrant. The level of sodium laurilsulphate is critical as it has been revealed from pharmacokinetic studies that this compound effects bioavailability. The lower acceptance criteria are based on bioavailability data and the upper acceptance criteria has been established so as to assure product quality.

Individual degradation products are controlled in compliance with VICH requirements. The proposal to exclude hardness from specification testing is accepted as it is tested on all batches during manufacture. Furthermore stability studies have revealed that apart for a slight decrease in hardness for tablets stored at 40°C/75%RH there is no tendency for a change in hardness during storage at long term conditions in the commercial package.

All analytical methods have been satisfactory validated i.e. demonstrated to be specific, linear, accurate, precise and robust. The HPLC method for determination and identification of the active substance and determination of related substances has been satisfactorily validated in line with VICH requirements.

Batch data are provided for batches used throughout development and for commercial manufacture. All data comply with the specification and at the same time justify the proposed specification. The levels of degradation products are consistently low (below the reporting threshold of 0.3%). Batch analysis data from batches manufactured with the commercial formulation are presented which support the validity of the manufacturing method and the robustness of the formulation.

Stability Tests on the Finished Product

Stability data were provided for batches stored for 18 months at 25°C/60%RH and 30°C/65%RH as well as 6 months at 40°C/75%RH. At the time of the production of the registration stability studies the 6 mg tablet was not proposed for marketing but this decision was later changed and the 6 mg tablet is now part of the authorisation. An additional stability program for three batches of the 6 mg tablet is planned. Data from this ongoing study will not be submitted unless deviations from the specification occur.

The batches are tested for the proposed specification (appearance, assay, impurities, water content, and dissolution) and in addition, for hardness and microbiological purity. There is no sign of degradation for any parameter at any of the conditions apart for a slight decrease in hardness for tablets stored at 40°C/75%RH. Degradation products stay below the reporting threshold. The data from the supportive studies give the same information as the formal stability studies. Stress degradation studies reveal that the tablets are chemically stable. Photostability studies confirm that the product is not sensitive to light.

The proposed shelf life of 2 years for product stored in Al/Al blister with no special storage conditions was accepted. Further confirmatory stability data from production scale batches from the manufacturing site on accelerated and long term stability programmes according to an agreed bracketing protocol will be provided. A shelf-life of 2 years as packaged for sale, without storage restrictions was accepted.

OVERALL CONCLUSION ON QUALITY

Trocoxil has been developed as chewable tablets for once-a-month dosing for dogs. The tablets applied for are 6 mg, 20 mg, 30 mg, 75 mg and 95 mg.

The pharmaceutical development of Trocoxil has been satisfactorily accounted for. Properties of the drug substance and excipients have been discussed, the development of the manufacturing process including equipment, scale-up and search for critical process steps have been presented as has also an account for manufacturing campaigns carried out.

Mavacoxib drug substance is a white to off-white powder. The crystalline Form I is used for the formulation and is an anhydrous, non-solvated and non-hygroscopic form. The active substance is manufactured through a two-step synthesis and the starting materials are commercially available. The same synthetic route has been used for the manufacture of all batches of the active substance. The proposed specification, for the active substance, including parameter, procedures and analytical

validation has been discussed and are acceptable. Data confirm the stability of the substance, no sign of degradation is seen at any of the conditions studied and for the duration of the studies.

All strengths are manufactured from a common blend containing 5 % w/w of mavacoxib. The excipients have been selected for purposes as palatability, solubiliser, filler, compression aid, disintegrant and lubricant. Manufacture and scale up throughout developments is thoroughly accounted for. Conventional direct compression tablet manufacture has been used throughout development. The process and equipment used during development utilised the same principles as proposed for the commercial process. Parameters considered are the particle size of the drug substance and furthermore those related to the instrumentation and equipment. The robustness of the proposed commercial process has been confirmed through qualification studies. In these studies different process parameters as e.g. blend speed, blend time and screen size has been investigated in combination with each other and also have interaction effects been evaluated. No critical steps have been identified. Batch data for several batches are in accordance with the specification.

The proposed specification, for the chewable tablets, including parameter, procedures and analytical validation has been discussed and is considered acceptable. As for the drug substance the stability studies performed (according to VICH requirements) show no sign of degradation.

Stability data under VICH conditions has been presented for three pilot scale batches of active substance and support a re-test period of 36 months. Stability data for the final product as packed in the packaging proposed for marketing supports a shelf-life of 2 years. The company agreed to place batches on a stability programme according to an agreed bracketing protocol. It has been demonstrated that changes in stereochemical purity do not occur on storage. A shelf-life of 2 years without storage restrictions, except that the product shall be stored in the original container as it is light sensitive, was approved.

Overall the documentation on quality relating to both mavacoxib drug substance and the drug product Trocoxil 6 mg, 20 mg, 30 mg, 75 mg and 95 mg chewable tablets for dogs, is of satisfactory quality.

3. SAFETY ASSESSMENT

Pharmacokinetics

The pharmacokinetics of mavacoxib was investigated in a GLP compliant study in rats following a single i.v or p.o dose at 5 mg/kg. The bioavailability of mavacoxib in the rat was high following a single oral dose. Mavacoxib was extensively distributed and the total body clearance relatively low. The half-life of mavacoxib following either oral or IV administration was 28-31 hours. The bioavailability of mavacoxib in the rat was high following a single oral dose. Mavacoxib was extensively distributed and the total body clearance was low. With increased dosing the C_{max} and AUC increased more than proportional. Following daily repeat exposure there was a marked increase in C_{max} and AUC from Day 1 to Day 7.

A validated LC-MS/MS bioanalytical method was used in the analysis of mavacoxib plasma concentrations in studies where blood samples were drawn for pharmacokinetic analysis. The absolute bioavailability was approximately 50 % in fasted conditions, and approximately 90 % in fed conditions. In a 70 day dose proportionality study, proportionality with respect to maximal concentrations and exposure was concluded for doses between 2, 4 and 12 mg/kg. Further safety studies seem to indicate that linearity prevails also at higher doses, even at 50 mg/kg (at least for maximal concentrations). A multiple dose study investigating the pharmacokinetics after repeated dosing showed that steady state was reached after approximately the second dose and no time dependent pharmacokinetics was evident.

The protein binding of mavacoxib is high, approximately 98 %. The highest tissue/plasma concentration ratio was in bile, having a value of 13. The applicant states that mavacoxib may undergo enterohepatic recycling. The volume of distribution is rather high, approximately 1.5-2 L/kg.

Study of the absolute bioavailability of mavacoxib and the effect of feeding on the bioavailability of orally administered mavacoxib in beagle dogs

The objective of this study was to determine the absolute oral bioavailability and effect of food within the gastrointestinal tract on the oral bioavailability of mavacoxib. Administration with food compared to fasted conditions resulted in an increase in bioavailability of 89.5%. The recommendation in the SPC is to administer the product with or before food. Without food, the bioavailability is approximately 50 % (30-60 %). After oral administration in fed conditions, the half-life is approximately 15 days. From a pharmacokinetic point of view, this supports a dose frequency of 28 days. It should however be noted that this is the half-life obtained in healthy dogs, and much longer half-lives have been observed in field studies on patient dogs.

Bioequivalence of orally administered mavacoxib flavoured tablets in dogs

Due to the poor solubility of mavacoxib, the size of the bulk drug crystalline particles may affect dissolution in the gastrointestinal tract and the resulting absorption of the drug. The primary objective of this study was to determine if an orally administered mavacoxib flavoured tablet containing bulk drug milled to a diameter of the 90th percentile (D90) of 57 µm had similar relative bioavailability to a reference mavacoxib flavoured tablet containing bulk drug milled to a D90 of 10 µm. The formulation used in the product has a bulk drug mill size of just below 60 µm. The two formulations were similar based on the modified bioequivalence criteria; however the results did not comply with the usually accepted bioequivalence criteria.

Multiple-dose study in beagles to evaluate the pharmacokinetics of mavacoxib 4 mg/kg orally by tablet on study days 0, 14, 42 and 70

The objective of this study was to determine the multiple-dose pharmacokinetics of mavacoxib. There did not seem to be any indication of time-dependent pharmacokinetics. The somewhat higher exposure after the second and third dose is expected based on the posology (14 day interval followed by a 28 day interval).

Distribution and excretion of ^{14}C-mavacoxib in dogs after a single 4 mg/kg oral or i.v. dose

The objective of this study was to characterise the extent and routes of elimination of ^{14}C-mavacoxib residues for 26 days after a single oral or IV administration, and to quantify the total ^{14}C-residues in selected tissues at 26 days following a single ^{14}C- mavacoxib IV or oral dose to help characterise the distribution of the drug. A secondary objective of this study was to characterise the pharmacokinetics of mavacoxib after oral and IV administration.

The bioavailability of the oral solution formulation was estimated to be 96.7% in this study. There was no appreciable accumulation of mavacoxib related metabolites in plasma. The mean total ^{14}C-mavacoxib related residues recovered in faeces and urine was 45.3% and 39.7 % of the dose for both treatment groups. Of the total amount recovered in each group, 37.1% and 8.2 % (T01) and 32.1% and 7.6 % (T02) was recovered in the faeces and urine, respectively.

Selected tissues and fluids were collected from all animals on day 26 of this study. ^{14}C-mavacoxib related residues were widely distributed in tissues and fluids in the dog after both administration routes. A majority of the tissues collected had mean tissue/plasma concentration ratios greater than 1. These included bile, mesenteric lymph nodes, spinal cord, brain, skin, whole blood, white fat, skeletal muscle, heart, liver, kidney, pancreas, adrenal glands, and all regions of the GI tract. Bile had the largest observed ^{14}C-mavacoxib related residue concentrations, with mean bile/plasma ratios of approximately 13. There were no apparent differences in the distribution or mean concentrations of ^{14}C- mavacoxib residues between the IV and oral treatment groups. The mean estimated total recovery of ^{14}C- mavacoxib and metabolites was 86.8% and 83.1% for animals in the two treatment groups.

Taking into account some study design limits (sampling up to 26 days), together with the tissue estimations, the majority of the dose was recovered after oral and intravenous administration. Although there are no exact figures of the total amount that would be excreted in faeces and urine respectively, it can be concluded, based on the data presented, that the majority is likely to be excreted in the faeces. The metabolites present have been identified in another follow-up study. The bioavailability determined should be interpreted with caution, given the limited sampling time. It is known that the absolute bioavailability of mavacoxib is high (approximately 90%) after fed conditions. The indication of a very high bioavailability in this study (96%), although the animals were fasted, may be related to the fact that an oral solution was administered in this study, compared to the tablets that may be burdened by solubility problem which is possibly improved by concomitant food administration.

Profiling of 14C-mavacoxib related residues in dog urine, faeces and bile

The objective of this study was to profile the ^{14}C- mavacoxib related residues in dog urine, faeces and bile collected in the distribution and excretion study. Mean total recoveries of ^{14}C-residues in the HPLC samples were 78.9%-83.1% in bile, 80.1%-86.0% in faeces, and 80.7%-91.8% in urine.

^{14}C- mavacoxib related metabolites were detected in all bile, faecal and urine samples. The majority of the metabolites detected eluted prior to the parent. In general, the profile of ^{14}C- mavacoxib residues detected in the excreta of dogs was found to be largely independent of dose route and time after dosing. Approximately 90 % of the fraction of the dose (8 %) that was excreted in urine consisted of metabolites. This means that approximately 1 % of the dose is excreted unchanged in the urine. Approximately 60 % of the dose was excreted as parent in the faecal extract after oral administration, i.e. approximately 50 % of the total administered dose, since approximately 80 % was recovered in total in faeces. CVMP concluded that the metabolites formed are likely to be of minor systemic toxicity importance given the high percentage of parent compound in plasma (≥96.5%).

In vitro assessment of protein binding for mavacoxib in canine plasma

The objective of this study was to determine the extent of protein binding by mavacoxib to canine plasma proteins. Recoveries of mavacoxib decreased with increasing dosing concentration due to

binding to the apparatus in the PBS compartment. However, as binding of mavacoxib was reversible; varying recoveries did not have a significant effect on protein binding. The degree of protein binding was high at all concentrations studied. Although protein binding interactions affecting mavacoxib is not that likely, mavacoxib may affect other highly protein bound substances to a clinically relevant extent.

Development of a Population Pharmacokinetic Model for mavacoxib in Dogs based on Data from Laboratory Animal Studies

The purpose of this work was to develop a population pharmacokinetic (PK) model for use in the design of the population pharmacokinetic component of a field trial with mavacoxib. This report describes the development of the population PK model, which was based on one laboratory efficacy study and three safety studies where the animals (young beagle dogs) received repeated doses (dose interval 2 or 4 weeks) ranging from 0.5 to 20 mg/kg. The final data set used data from the three studies where the dose was given as a tablet (a laboratory efficacy study and two safety studies) contained 616 concentration records from 86 dogs. The doses were administered following overnight fast in the laboratory efficacy study, but in the other studies the dogs were allowed access to food around the time of dosing. The model was developed using NONMEM (version V) employing the first order conditional estimation method with interaction.

The data were described by a one-compartment model with first order absorption. In one of the safety studies the blood sample collection was rich, thus allowing for the estimation of the absorption rate constant (KA) in addition to oral clearance (CL/F) and oral volume of distribution (V/F). In all the other studies mainly trough samples were collected and therefore KA was fixed in the final model to the value obtained in one of the safety studies. A sensitivity analysis showed that this approach was acceptable. The typical CL/F and V/F in the final model were 0.104 L/day/kg and 2.29 L/kg, respectively, resulting in a typical half-life of 15.3 days. Relative to the fed state, fasting resulted in a 22% reduction in bioavailability. The interindividual variability in CL/F and V/F was 36% and 21%, respectively. In addition, inter-occasions variability for F was estimated to 22%. The residual variability was low, 10.3%.

In preparation for the population PK modelling of the field study simulations were performed based on the final model using the following regimen; 4-5 mg/kg with a 14 day interval between the first two doses but with a 30 day dosing interval thereafter. Little fluctuation was predicted in trough plasma mavacoxib concentrations over the course of treatment. Median trough plasma mavacoxib concentrations after the first and fourth doses, with all doses administered to fed dogs, were predicted to be 1065 and 807 ng/ml, respectively. Few trough concentrations were predicted to exceed 2000 ng/ml. The simulations also showed that applying a model neglecting the absorption (i.e. assuming a bolus dose was administered) would result in adequate estimation of CL/F and V/F.

CVMP concluded that the population analysis in this study has in general been well performed and reported. The goodness-of-fit plots reveal a tendency for under-prediction of high concentrations following high doses and/or late time points, which may be an indication of an overprediction of CL/F.

Population Pharmacokinetic Analysis of Plasma Mavacoxib Concentration Data from EU field safety and efficacy study

This report describes the development of a population PK model based on data from the European Canine field safety and efficacy study in client-owned osteoarthritic (OA) dogs (several breeds included). The dogs were treated with 4 mg/kg on day 0, approximately day 14 and then approximately monthly for five more doses. Trough blood samples were obtained from 224 animals. The modelling did not take into account whether the drug had been taken with or without food. The model was developed using NONMEM (version V) employing the first order estimation method.

The data were described with a one-compartment model where CL/F and V/F were related to body weight (body weight ranged from 4.6 to 67 kg) applying a power model with an estimated exponent of 0.93, i.e. almost linear. In addition, age had some impact on CL/F. However, the age effect was not as

strong as the body weight effect and may not have been adequately estimated as the main part of the animals were elderly (<7% of dogs younger than 5 years, median age being 10 years). Further, a few animals (<5%) had a much lower CL/F, which could not be explained with any of the available covariates. Therefore, a mixture model was applied allowing for estimation of a separate CL/F for those animals. Typical CL/F was estimated to 1.53 and 0.583 L/day (for a dog weighing 35 kg, being 10 years) for the two groups of dogs with rapid and slow (5% of the population) elimination. Typical V/F was estimated as 90 L (for a dog weighing 35 kg). The resulting half-life was 41 and 107 days for rapid and slow elimination groups, respectively. The interindividual variability in CL/F and V/F was 42% and 25%, respectively. The residual variability was 15.8%. Goodness-of-fit plots are provided.

In summary, with respect to covariate model building, a conclusion may be drawn for those covariate relationships tested within NONMEM, i.e. body weight, age, CRT, AST, WBC and sex. For covariates not identified from graphical screening (BSA, ALT, ALP, BUN, bilirubin, breed category, class of concomitant medication) it cannot be concluded that those do not have an effect unless the shrinkage of the empirical Bayes estimates are presented. Further, for a claim in the labelling of no effect it is needed to include the covariate in the NONMEM model and assess the confidence interval for the effect with an appropriate method (e.g. bootstrap method).

It was stated that plasma concentrations below the limit of quantification (BLQ) were set to 0 and included in the analysis. In the new population pharmacokinetic analyses in which data from the previous studies were pooled with new data from studies (field safety and efficacy study at a dose of 2 mg/kg bw) and plasma samples obtained at prolonged intervals after the last mavacoxib administration, the dataset contained 1317 concentration samples from 286 dogs. Approximately 3% of the samples had concentrations that were BLQ. The CVMP concluded that appropriate steps have been taken to avoid the introduction of severe bias arising from samples below the limit of quantification and that the applicant has investigated several methods for handling data BLQ in the new analysis and chosen the one appearing most appropriate.

The goodness-of-fit plots from one study indicate an over-prediction of low concentrations. The possibility of over-prediction of low concentrations because of an unusually long estimate for half-life and an unusually low estimate for CL/F can be ruled out. Based on the information presented CVMP concluded that there does not appear to be an obvious trend for the incidence of overprediction of low concentrations with regard to subject demographics, mavacoxib dose, or time of the samples. In all of the population PK modelling conducted thus far, the vast majority of observations were fitted very well by the models and the few over-predictions of low concentrations are not likely to represent an important model misspecification.

The CVMP accepted that both population PK models; the laboratory Beagle model and the osteoarthritic (OA) model; are correct and that the PK differences between the models may be due to differences between the populations in body weight and age. Additional population PK modelling work was performed. The new population analysis based on data from the two field studies (for the 4 mg/kg dose and the 2 mg/kg dose) is well performed. Appropriate methods taking observations BLQ into account has been used, shrinkage towards the population parameter estimates was shown to be low for CL/F and V/F and the outcome is acceptable.

Thereafter, the new population PK model was developed based on all data, and the covariate effects described were established. In addition, to account for the difference in CL/F between the studies, the bioavailability, F, was estimated to be 25% lower in the 2 mg/kg study. This result was unexpected as the drug was taken with food in the 2 mg/kg study (uncontrolled food intake in the 4 mg/kg study) and food is known to increase the bioavailability. The Applicant has no definitive explanation but speculates that it could be due to a dose-dependent difference in CL/F, but this has not been indicated in other studies. The goodness-of fit indicate some over-predictions of low concentrations which may be in line with a non-linear CL.

The established covariate model predicts an effect of body weight (the most important), age and breed, and the model predicts that body weight adjusted CL/F (i.e. in L/day/kg) is higher in small and young animals. Compared to a typical dog (10 years and 35 kg, not German Shepherd/Labrador) the AUC

following a 2 mg/kg dose will be approximately 35% lower in a 10 year old-dog weighing 5 kg and approximately 55% lower in 1 year-old dog weighing 5 kg.

Population kinetics demonstrated a quite large weight- and age-dependent difference in clearance suggesting that younger and lighter dogs may require a higher dose per kg BW to obtain sufficient exposure. Furthermore, most of the dogs included in the field studies were mainly of higher weights and age. Based on these findings the CVMP questioned whether dose recommendations should be adjusted according to PK findings.

Of the 286 client-owned dogs suffering from osteoarthritis (OA) for which empiric Bayes estimates (EBEs) are available for mavacoxib PK parameters, 11.5% had baseline ages ≤ 5 years and 8.4% had baseline body weights ≤ 15 kg. Only two dogs were younger than 5 years and had body weights of less than 15 kg.

However, because of the very small number of light and young OA patients in the two field trials and the extrapolation necessary for the prediction of PK in light young patients with the OA population PK model, the 2 mg/kg dose is applied to all patients. If data subsequently become available to indicate that a higher dose is more effective in light young patients, the applicant would then recommend a higher dose for such patients. The applicant demonstrated that light, young OA patients will achieve lower systemic exposure of mavacoxib. There are limited pharmacokinetic data for these patients, and parts of the pharmacokinetic conclusions are dependent on information from laboratory Beagle dogs. There may be genetic influences not yet identified influencing mavacoxib pharmacokinetics and the largely unexplained variability (not due to age and body weight). Furthermore, there is limited data with respect to efficacy and safety for this sub-population, but there are no signals of inefficacy in this group. Thus, the CVMP agrees that the 2 mg/kg dose is safer to use at present and accepts that no differentiation of dose depending on age and weight is recommended.

The population analysis in the PK model study identified a group with lower elimination, which could not be explained by available covariates. The explanation for the large between-subject variability in PK is speculative at this time. The primary route of mavacoxib elimination is faecal excretion of intact drug, and possible explanations for variable clearance related to this pathway could include variability in hepatic uptake, biliary transport, or enterohepatic recirculation of parent mavacoxib excreted in bile. Several canine cytochrome P450 isoforms appeared capable of catalysing mavacoxib oxidation. This suggests that polymorphic enzymes or variable enzyme expression would be less likely to contribute to metabolism differences due to the presence of redundant metabolic pathways. Based on what is known about mavacoxib PK, variability in plasma protein binding, renal clearance, and metabolism do not appear to contribute substantially to variability in mavacoxib PK.

The Applicant has provided information about the variability in the half-life of mavacoxib. The animals with the estimated long half-lives are of varying ages and body weights and no explanatory factor to identify animals with the extreme half-lives has been provided. CVMP proposes to allow a maximum of seven consecutive doses in order not to reach too high plasma concentrations in animals with this long half-life.

A typical dog with a half-life of 30 – 40 days will reach steady-state following 5 to 7 months and the steady-state plasma levels will be approximately doubled compared with a single dose if dosed every month. However, for a dog with a half-life of 80 hours the time to reach steady-state will be approximately 13 months and the steady-state levels will be approximately 4 times higher compared with a single dose if dosed every month. Even if dosing is stopped following the 7th dose, approximately 90% of steady-state concentrations will be reached at this time. If the cause for the prolonged half-life is due to changes in clearance, the steady-state levels will be considerably higher (2-3 times higher) compared with an animal with a typical half-life. Similar calculations based on linear, time-independent one-compartment pharmacokinetics can be done for alternative half-lives.

The reduction in dose in one field safety study to 2 mg/kg doubles the therapeutic index for the product, adding to the benefit of sustained therapeutic efficacy. The reduction in plasma levels is presumed to have a beneficial impact on the safety and efficacy of mavacoxib. The applicant also put

forward the fact that the incidence of adverse events at the lower dose (2 mg/kg) was similar in the two treatment groups, with a lower incidence of serious suspected adverse events for mavacoxib. Clinical chemistry is claimed to be unremarkable, with no evidence of a protein losing enteropathy or changes in renal parameters. Furthermore, Mavacoxib has been tested in a 180-day GLP overdose safety study. In this study, the applicant claims that safety was demonstrated at 15 mg/kg for 180 days which suggests a 6-fold safety margin for the dose (2 mg/kg).

Monte Carlo Simulation of Mavacoxib Trough Plasma Concentrations in Support of Mavacoxib Dosage Recommendation in the Treatment of Pain and Inflammation Associated with Osteoarthritis in Dogs

This report describes a series of Monte Carlo simulations on the basis of the final model aiming to i) recommend dosage adjustment based on body weight of animal patients, ii) explore the effect of food on mavacoxib trough plasma concentrations in dogs when Trocoxil oral tablets are administered after a meal during the whole treatment period and iii) explore the influence of possible inconsistent drug administration with food on PPK model.

In the first simulation the drug exposure following the proposed dosage regimen was simulated in a large population. A dose regimen of 2-2.5 mg/kg (first dose interval 15 days, thereafter 30 days) was administered to 5000 dogs with weight and age distributions similar to those in the field study. The simulations were performed using the model called the Stage Two final population PK model but changing the effect of food to four simulation scenarios: the oral bioavailability under fed conditions was assumed to be 0%, 30%, 60% or 90% greater than during fasting conditions. Percentages of animals with predicted trough concentrations <0.4 μg/mL or < 5 μg/mL, which is an arbitrarily selected therapeutic window, were presented. It was shown that under the worst case scenario with respect to adverse effects (food effect of 90% increase in oral bioavailability), 4.5% and 6.7% of the animals would reach through concentration above 5 μg/mL following the 7^{th} and 13^{th} dose, respectively. For the worst case scenario with respect to efficacy (food effect of 0% increase in oral bioavailability), 2.6% and 2.5% of the animals would reach through concentration below 0.4 μg/mL following the 7^{th} and 13^{th} dose, respectively.

A second series of simulations were performed to assess whether the obtained longer half-lives observed in the main field study possibly could be explained by not taking into account an inconsistence in food intake within a dog in the population modelling. A dose regimen of 4-4.5 mg/kg (first dose interval 15 days, thereafter 30 days) for a total of seven doses was administered to 250 dogs. The simulations were performed using a model similar to the one called the Stage One final population PK model. However, the mixture part of the model was not included. Further, it was assumed that the first five doses were administered without food and for the last two doses, food was administered in 50% of the dogs. The effect of food was according to four scenarios: the oral bioavailability under fed conditions was assumed to be 0%, 30%, 60% or 90% greater than during fasting conditions. Each scenario was simulated 250 times, followed by a re-estimation of the population parameters using the model without any food effect to assess the possible bias in parameters estimates obtained by not accounting for food intake. The results of these simulations showed that CL/F was downward biased (-27% worst case) and V/F upward biased (18% worst case), thus resulting in an increased half-life (on average 66 days), if the information about administration with/without food was not gathered during the trial and included correctly during population PK modelling. However, the conclusion of the report is that the findings of the simulation, when viewed in context with previous PPK modelling, suggest that mavacoxib was, in general, consistently administered without food to OA dogs during the main field study. That is, the applicant believes the longer half-life observed in the field study to be more accurate.

If the simulations should be used as support for the dosing recommendation, a visual predictive check (VPC) is required for the model used in order to feel confident that simulations predict the observations well. Preferably also a numerical predictive check should be presented. The proposed therapeutic window used to assess the drug exposure following the dosage 2-2.5 mg/kg has been set arbitrarily and has not been developed on adequate analysis of concentration versus clinical efficacy and adverse effects, respectively. Hence, simulations of the drug exposure as the only support for a

dosage recommendation that is different to that used in the pivotal clinical efficacy study (4-4.5 mg/kg) is not sufficient to prove that the dose has a positive benefit-risk ratio.

The discrepancy in the CL/F and thereby half-lives reported for laboratory animals and OA dogs, can possibly to some extent be explained by not taking an inconsistent food intake into account in the modelling, as shown by the simulations in this study. However, theoretically the change in bioavailability should not change the half-life of the drug, but possibly due to only having trough samples the model may be misspecified as observed. A possible remedy to the problem in the field study would have been to apply an inter-occasion variability term to the bioavailability parameter F, which actually was used in the initial population PK model.

Toxicological studies

Single dose toxicity

Single dose oral and dermal toxicity was studied in the rat. In addition, an acute oral tolerance (see Part 4) study was carried out in beagle and mongrel dogs to determine the potential acute toxicity of mavacoxib.

An acute oral toxicity study was conducted in Sprague-Dawley rats who were orally administered an aqueous methylcellulose vehicle containing mavacoxib at a single dose of 2000, 500 or 50 mg/kg body weight. Clinical signs of toxicity were observed in animals dosed with 2000 and 500 mg/kg and included ataxia, cage biting, distended abdomen, deep sleep, dyspnoea, presence of material around the eye(s), eyelid squinting, gasping, increased salivation, lacrimation, lethargy, moribundity, decreased or no stool, staining of the urogenital area, recumbency and unkempt appearance. At 50 mg/kg no rats died and necropsy revealed no remarkable findings at the 14-day terminal sacrifice. Mavacoxib would be classified as moderately toxic, as an oral dose of 500 mg/kg produced harmful effects in rats.

The acute dermal toxicity was evaluated in the rat in accordance with OECD Guideline 402 Acute Dermal Toxicity and the Commission Directive 92/69/EEC. There were no deaths, signs of systemic toxicity, signs of dermal irritation, or abnormalities at necropsy noted. Two females showed no gain in bodyweight during the second week. The acute dermal median lethal dose (LD_{50}) of mavacoxib was greater than 2000 mg/kg bodyweight.

Repeated dose toxicity

Repeat dose toxicity was studied in the rat following daily oral administration and in the dog as part of the tolerance in the target species documentation (see Tolerance part 4).

A one month oral toxicity study of mavacoxib in rats with one month of recovery at doses of 0 (saline), 5, 15 and 25 mg/kg/day was conducted, in a GLP compliant study. Due to mortality, treatment was discontinued after 13-15 days and the surviving animals were allowed to recover until terminal sacrifice on day 29 or until an additional 1-month treatment-free period. Oral administration of mavacoxib to rats at 5, 15 or 25 mg/kg/day produced marked toxicity. Mortality due to gastrointestinal ulceration was observed in all treatment groups, leading to discontinuation of dosing after two weeks. At cessation of treatment, the toxic effects resolved slowly. In addition to gastric ulceration and peritonitis a number of organs were affected. These changes were considered as secondary to gastrointestinal ulceration, deteriorated health status and resulting stress. Still, the extensive gastrointestinal toxicity and its secondary effects could have masked unrelated organ specific toxicity. Renal papillary oedema, centrilobular hepatocellular hypertrophy, hypertrophy of the thyroid gland, vacuolated cells in the pars distalis of the pituitary were observed in surviving animals without gastrointestinal and abdominal lesions at 5 mg/kg. Rats were exposed to plasma drug concentrations that markedly increased with time, suggesting accumulation of compound. A No Observed Adverse Effect Level (NOAEL) was not identified in this study. It can be concluded that following repeat daily administration of mavacoxib to the rat accumulation leading to marked toxicity and mortality will occur. The long half-life is of user safety concern since a single accidental oral

exposure has the potential to lead to prolonged exposure time. The long-term toxicity of mavacoxib was evaluated from the studies performed in the target species. This is acceptable for a product intended for use in non-food species only.

Reproductive toxicity, including teratogenicity

No studies to examine the effects of mavacoxib on reproduction were conducted. The safety in breeding animals has not been demonstrated. As a consequence, a warning regarding use in breeding animals is given in the SPC section 4.7.

Embryotoxicity/foetotoxicity, including teratogenicity

No studies to examine embryotoxic/foetotoxic effects of mavacoxib were conducted. The lack of reproductive and embryo/foetotoxicity studies is acceptable for a product intended for use only in non-food producing animals provided that the product is not intended for use in pregnant and breeding animals.

From the extensive experience of the use of NSAIDs (including COX-2 inhibitors) it is known that inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies (humans) suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. Due to the risk of cardiopulmonary toxicity, renal dysfunction of mother and neonate, possible prolongation of bleeding time, and inhibition of uterine contractions NSAIDs (including COX-2 inhibitors) are contraindicated in humans during the third trimester of pregnancy.

In laboratory animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. Appropriate statements are included in the SPC sections 4.3 and 4.7

Mutagenicity

Mavacoxib was tested in a standard battery of genotoxicity tests as recommended in VICH GL23 and in GLP-compliance. No evidence of genotoxicity was observed.

A bacterial reverse mutagenicity test was conducted in the recommended strains of *Salmonella typhimurium* and *Escherichia coli* in either the presence or absence of a metabolic activation system. Mavacoxib was considered to be non-mutagenic under the conditions of the test. A chromosomal aberration assay was conducted with primary human lymphocyte cultures and evaluated in either the presence or absence of a metabolic activation system. Mavacoxib was negative for inducing structural or numerical chromosome aberrations in human peripheral lymphocytes with or without metabolic activation when tested up to cytotoxic concentrations. An *in vivo* micronucleus test was conducted in rats orally administered mavacoxib and the bone marrow of treated rats was evaluated for increased frequency of micronucleated polychromatic erythrocytes. Mavacoxib was not clastogenic in rat bone marrow when tested up to the maximum tolerated dose of 400 mg/kg for 2 days.

Carcinogenicity

No carcinogenicity studies were performed with mavacoxib. Mavacoxib did not show any genotoxicity potential in a standard battery of GLP-compliant tests. In accordance with the Annex I of Council Directive 2001/82/EC carcinogenicity is not required if the following 3 criteria apply: i) No close chemical analogy with known carcinogens; ii) Negative mutagenicity test and, iii) No suspect signs during toxicity testing.

Studies of other effects

A local lymph node assay in the mouse was conducted where female mice were exposed to daily applications (to the dorsal surface of each ear) of mavacoxib as a solution in dimethyl formamide in a GLP compliant study. Mavacoxib was considered to be a non-sensitiser under the conditions of the test.

A **Skin sensitisation study of mavacoxib in albino guinea pigs** was conducted where Hartley albino guinea pigs was dosed topically with Mavacoxib once per week for 3 weeks in a GLP compliant study. Under the conditions of this study, mavacoxib was a non-sensitiser in albino guinea pigs.

A **Local tolerance study in the male rabbit after dermal administration** was conducted where two skin sites, one abraded and one intact, on the backs of male albino New Zealand White rabbits received a semi-occlusive application of mavacoxib powder moistened with sterile water to form a paste in a GLP compliant study. No mortality or clinical signs of systemic toxicity were observed for either rabbit at any time during the 14-day observation period. Mavacoxib was slightly irritating to the intact and abraded skin.

A **Local tolerance study in the male rabbit after ocular administration to the** eyes of male albino New Zealand White rabbits instilled with mavacoxib bulk drug powder in a GLP compliant study showed no mortality or clinical signs of systemic toxicity for either rabbit at any time during the 14-day observation period.

The skin sensitisation and skin and eye irritation potential of mavacoxib (as solution or bulk drug powder, not the final formulation) was investigated in a battery of well conducted GLP compliant studies. Mavacoxib was a non-sensitiser, slightly irritating to intact and abraded skin, and minimally irritating to the eye. Although mavacoxib is not used in humans, because its chemical structure is similar to non-arylamine sulphonamides, a warning in section 4.3 of the SPC is included: 'Do not use in cases of known hypersensitivity to sulphonamides'.

Observations in humans

No studies to examine the effect of mavacoxib on humans were performed.

Microbiological studies (studies on human gut flora and organisms used in food processing)

No microbiological studies were conducted. This is accepted since Mavacoxib is indicated for use in dogs only (non food-producing species).

Studies on metabolites, impurities, other substances and formulation

There were no studies conducted on metabolites, impurities or other substances.

User Safety

A satisfactory User Safety Assessment in accordance with the Guideline on User Safety (EMEA/CVMP/543/03-Final) comprising of an exposure assessment, hazard identification and risk characterisations for identified exposure scenarios was conducted. The toxicity of mavacoxib was evaluated in a series of nonclinical target animal safety studies, as well as toxicity studies. These included single-dose studies in rats and dogs; daily repeat-dose studies up to 15 days in rats; intermittent repeat-dose studies up to 6 months in dogs; *in vitro* and *in vivo* assays for genotoxic potential; and a battery of occupational worker safety studies (dermal toxicity, dermal irritation and sensitisation; and ocular irritation).

The tasks and situations identified as leading to exposure were limited to the administration of the tablet to the dog by a non-professional user (dog owner) and accidental ingestion. The routes of

potential exposure were limited to dermal contact, oral ingestion of trace amounts from hand-to-mouth transfer and oral ingestion of the product.

Accidental exposure to an adult administering the product via oral, dermal, or ocular exposure is minimal and would not be expected to represent a safety risk. Instructions for this product in the SPC which further protect the adult user include washing hands after handling of the product. In the case of a toddler trying to access the packaged product, the engineering design of the foil/foil blister packaging should provide protection.

The skin sensitisation and skin- and eye irritation potential of mavacoxib (as solution or bulk drug powder, not the final formulation) was investigated in a battery of well conducted GLP compliant studies. Mavacoxib was a non-sensitiser, slightly irritating to intact and abraded skin, and minimally irritating to the eye. These local toxicity studies should preferably be conducted with the final product (active substance plus excipients), alternatively the potential effects be deduced from data of the single ingredients. The excipients were briefly discussed in the User Safety Assessment and none were considered to be a human user safety concern, however, the sensitising and skin irritating potential of each excipient was discussed at the request of the Committee. The Applicant provided an adequate summary of the skin irritating and sensitising potential of the individual ingredients of the final formulation of Trocoxil. It is agreed that the final formulation is not expected to produce skin irritation or sensitisation to a person administrating the tablets to a dog.

The exposure scenario of most concern is the accidental ingestion of one 95 mg tablet by a 15 kg child (8 mg/kg). When applying an assessment factor of 10 to account for animal to human extrapolation there is no margin to the acute minimum symptomatic dose of 25 mg/kg observed in dogs. This dose is however not accepted as a NOAEL, as gastric ulceration was observed also at this dose. The risk characterisation should have been based on the repeat dose NOAEL (15 mg/kg) and maybe also taking into account unwanted pharmacological effects. The long half-life of mavacoxib observed in dogs is of concern since a single accidental exposure has the potential to lead to prolonged exposure time resulting in adverse gastrointestinal and renal, or pharmacological effects during several weeks.

In addition to the child-proof packaging, a warning has been added to section 4.5 of the SPC in order to avoid accidental ingestion by a child. "Ingestion of Mavacoxib can be harmful for children, and prolonged gastrointestinal and pharmacological effects may be observed. To avoid accidental ingestion administer the tablet to the dog immediately after removal from the blister packaging."

Environmental Risk Assessment

An environmental impact assessment in accordance with the CVMP Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products- Phase I (CVMP/VICH/592/98-Final) was conducted. Given that Trocoxil tablets are intended for use in non-food animals only, then the Phase I assessment for this VMP may stop at Phase I. It can be concluded that the proposed use of mavacoxib in dogs is unlikely to result in an unacceptable environmental impact.

Conclusion on safety

The population pharmacokinetic characteristics were described in laboratory animals and in client-owned osteoarthritic (OA) dogs included in the European Canine field safety and efficacy study. In the model describing the field study data, the most important covariate effect was body weight which was almost linearly related to CL/F and V/F. In addition, age had some impact on CL/F. A small proportion (5% of the population) was identified to have a reduced CL/F and this phenomenon could not be explained by any available covariate.

The bioavailability of Mavacoxib in the rat was high following a single oral dose. Mavacoxib was extensively distributed and the total body clearance was low. The t½ was 28-31 hours following oral and i.v. administration. With increased dosing the C_{max} and AUC increased more than proportional. Following daily repeat exposure there was a marked increase in C_{max} and AUC from Day 1 to Day 7. This is not surprising when considering the long half-life of mavacoxib, which does not support a

repeat daily dosing regimen. In the dog, after oral administration in fed conditions, the half-life of mavacoxib was approximately 15 days.

In the 1-month repeat dose toxicity study in the rat marked gastrointestinal toxicity leading to mortality in all dose-groups resulted in discontinuation of dosing after two weeks. In addition to gastric ulceration and peritonitis, a number of organs were affected. These changes were considered as secondary to gastrointestinal ulceration, deteriorated health status and resulting stress. Still, the extensive gastrointestinal toxicity and its secondary effects could have masked unrelated organ specific toxicity. Renal papillary oedema, centrilobular hepatocellular hypertrophy, hypertrophy of the thyroid gland, vacuolated cells in the pars distalis of the pituitary were observed in surviving animals without gastrointestinal and abdominal lesions at 5 mg/kg. A NOAEL was not established. It can be concluded that following repeat daily administration of mavacoxib to the rat accumulation leading to marked toxicity and mortality will occur. The long half-life is of user safety concern since a single accidental oral exposure has the potential to lead to prolonged exposure time.

The acute oral and dermal toxicity was sufficiently documented in the rat in GLP-compliant studies. Mavacoxib was of moderate acute oral toxicity with a minimal lethal oral dose established at 500 mg/kg in both male and female rats. The dose of 50 mg/kg can be retained as NOAEL. The dermal bioavailability was not determined; however the low acute dermal toxicity at the limit dose (2000 mg/kg) suggests low dermal absorption. The acute dermal LD_{50} was greater than 2000 mg/kg. In an acute oral tolerance study in dog there were no deaths at doses ≤ 50 mg/kg; the results demonstrate the potential for development of gastrointestinal adverse events by a single dose of 25-50 mg/kg.

The tolerance was explored in single and repeat dose studies using treatment intervals appropriate for a compound with this long half-life. In dogs, as expected from an NSAID, the main findings were changes related to the gastrointestinal tract, and to a less extent also to the kidney. For these effects, a dose of 4 mg/kg is considered the reference dose in order to elaborate the user safety assessment.

The lack of reproductive and embryo/foetotoxicity studies is acceptable for a product intended for use only in non-food producing animals provided that the product is not intended for use in pregnant and breeding animals.

In laboratory animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. The following wording is added to Section 4.7 of the SPC: "Do not use in pregnant, breeding, or lactating animals. Studies in laboratory animals administered a prostaglandin synthesis inhibitor have shown increased pre- and post-implantation loss, embryo-foetal lethality, and malformations."

Mavacoxib did not show any genotoxicity potential in a standard battery of GLP-compliant tests. The lack of carcinogenicity studies is acceptable. Mavacoxib is not used in humans; because it chemical structure similar to non-arylamine sulphonamides a warning in the SPC is included.

The skin sensitisation and skin- and eye irritation potential of mavacoxib (as solution or bulk drug powder, not the final formulation) was investigated in a battery of well conducted GLP compliant studies. Mavacoxib was a non-sensitiser, slightly irritating to intact and abraded skin, and minimally irritating to the eye. The sensitising and skin irritating potential of each excipient was discussed in detail at the request of the CVMP.

A satisfactory User Safety Assessment was conducted. It was agreed that the risk from exposure is negligible due to the low dermal absorption and low toxicity of mavacoxib. The exposure scenario of most concern is the accidental ingestion of tablets by a 15 kg child. A NOAEL was not identified in the acute oral toxicity study in dog (< 25 mg/kg).

An environmental impact assessment in accordance with the CVMP Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products- Phase I (CVMP/VICH/592/98-Final)

was conducted. A Phase I Environmental Impact Assessment is acceptable and Trocoxil is unlikely to result in an unacceptable environmental impact.

4. EFFICACY ASSESSMENT

Mavacoxib - 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is used in the treatment of chronic pain and inflammation associated with osteoarthritis in dogs.

Pharmacodynamics

In a distribution and excretion study, the majority of the dose is most likely excreted in the faeces (sampling up to 26 days). The total recovery of the dose after radioactive profiling was approximately 80 % in faeces, urine and bile. Approximately 60 % of the total dose recovered was unchanged mavacoxib, i.e. approximately 50 %, and in urine, 1 % was excreted as unchanged mavacoxib. The applicant did however not identify the metabolites in relation to what has been evaluated toxicologically.

COX is a key enzyme in pathways of arachidonic acid metabolism. Its activity culminates in the synthesis of local hormones and inflammatory mediators, termed eicosanoids, which include several prostaglandins. COX-1 is a widely distributed constitutive enzyme, primarily involved in maintaining organ and tissue function, whilst COX-2 is inducible at sites of tissue damage but in some organs it is also constitutive. COX-2 exerts the major role in synthesising prostaglandins which have pivotal roles as mediators of pain, inflammation and fever. Mavacoxib acts by preferential inhibition of COX-2-mediated prostaglandin synthesis. It therefore possesses analgesic and anti-inflammatory properties. The products of COX-2 metabolism are also involved in ovulation, implantation and closure of the ductus arteriosus. Both COX-1 and COX-2 are present constitutively in the kidney and are assumed to possess protective roles in adverse physiological circumstances.

Determination of COX1 and COX2 inhibition (IC50s and ratios) for Carprofen and Mavacoxib in the canine in-vitro whole blood assay

An in-vitro study including a positive control (carprofen) was performed to explore the inhibitory potential of the active substance. COX-1 and COX-2 inhibition was determined using Cayman Chemical EIA kits- Thromboxane B2 for COX-1 activity and Prostaglandin E2 (PGE2) for COX-2. The results indicated that Mavacoxib is intermediately specific to COX-2 (IC_{50} geometric mean COX-2/COX-1 ratio: 21.2), and in this respect similar to carprofen (IC_{50} geometric mean COX-2/COX-1 ratio: 17.8). The health status of the dogs used in this study was certified annually prior to study start and has been confirmed weekly, thereafter, by visual observation. The validity of the whole blood assay used is highly dependent on the health status of the animals from which samples are collected.

Tolerance in the target species

Tolerance in the target species (dog) was explored in 9 different studies including in total 252 healthy young adult Beagle or mongrel female and male dogs. In two of these studies, treatment duration was according to what is suggested in the SPC but the lowest dose was twice the recommended (2 mg/kg) and dose levels were in between 4 mg/kg and 25 mg/kg. The target animal tolerance results indicate that in healthy young dogs, 50 mg/kg is connected to a high incidence of adverse events related to the GI tract. Furthermore, severe adverse events in the form of perforation of the gastrointestinal tract occur at 25 mg/kg. At 15 mg/kg dose level the frequency of gastrointestinal disturbances is increased as compared to placebo, but the incidence is generally low and mild in character at 4 mg/kg to 15 mg/kg. Dose dependent treatment related adverse events related to renal integrity are indicated, and occur at low frequency and magnitude even at 12 mg/kg. Since 2 mg/kg is the final agreed dose, the design of these studies with regard to dose levels and duration, is in accordance with the requirements for tolerance studies. As expected for an NSAID, the main findings from these studies were changes related to the gastrointestinal tract, emesis, diarrhoea and soft/mucoid faeces and to a lesser extent also to the kidney. Feed consumption and body weight seemed not to be affected by treatment. Both long and short term studies revealed an increase in blood urea nitrogen (BUN) concentrations after about one week of treatment, at 12 mg/kg dose levels. The level of increase was mainly of a moderate magnitude and a return to normal values was indicated in samples collected 2 months after the end of a

5 month long monthly treatment period. Suitable warnings to address the incidence and severity of adverse events are included in the SPC.

Clinical Studies

Dose determination studies

Five studies were initially presented to select and justify the proposed dose, which at time of study performance was 4 mg/kg. In 4 of them, the effect was explored in healthy beagle dogs after induction of an acute synovitis in the femorotibial, metacarpal or stifle joint, by use of cytokine containing media or Carrageenan. In the fifth study, a chronic osteoarthritis model was used on dogs of different breeds. Doses between 0.5 mg/kg and 8 mg/kg were explored. Dose determination studies demonstrated that in healthy Beagle dogs, by providing 4 mg/kg BW, a significant reduction of acute lameness is persistent for 22-28 days. At 2 mg/kg, the effect is at best significantly different from placebo for only 7 days after treatment. Similarly, 2 mg/kg administered in a chronic osteoarthritis model, was connected to a significant reduction in lameness for 2 weeks and weak support for any effect beyond that point. In the latter model, 8 mg/kg was connected to an effect-duration of 5 weeks. Based on the results from some studies on acute synovitis, the Mavacoxib plasma concentration 400 ng/ml was calculated as the cut-of level for clinical effect. In justifying the dose selected, additional data from a new clinical field safety and efficacy study where 2 mg/kg BW was used was provided. Analysis of this study revealed that the efficacy of monthly Mavacoxib administration at a dose of 2 mg/kg is again non-inferior to carprofen at a daily dose of 4 mg/kg. According to field data, non-inferiority to carprofen treatment was demonstrated both at the dose level 4 mg/kg BW and at the lower dose 2 mg/kg BW. To address the safety concerns to the extent possible, the lower of those two doses are recommended with some variability depending on tablet sizes available. These efficacy results substantiate that an initially proposed dose of 4 mg/kg is too high. These data also suggest a similar tolerance profile for the two products Trocoxil and carprofen.

Field trials

Determination of the efficacy and safety of mavacoxib oral tablets administered two times at 4 mg/kg, with the second dose following a loading dose interval of approximately 14 days, in the treatment of pain and inflammation associated with osteoarthritis in dogs

This study includes the phase from screening for inclusion up to the 5th assessment occasion (analysable time point 25 to 36 days post second dose of Investigational Veterinary Product) for all cases. The GCP study objective is to assess field efficacy and safety in the treatment of pain and inflammation associated with naturally occurring osteoarthritis, in comparison to a positive control. Four hundred and seventy four dogs of different sex and breeds, weighing between 4.4 and 67.0 kg and between one and 16 years old (T01 mean age; 9.1 years, T02 mean age, 9.0 years) were included from 15 clinics. This was a randomised multi-centre parallel group design with a positive control. Mavacoxib oral flavoured tablets, in the proposed commercial formulation (20 mg, 30 mg, 75 mg, 95 mg, 120 mg) and placebo: proposed commercial formulation without active substance were used. Carprofen tablets, 20 mg, 50 mg and 100 mg were used as the control and placebo for carprofen.
Dogs were divided into two groups and received:

T01 (Mavacoxib, N=226)	4 mg/kg of mavacoxib days 0 and 14 Placebo for carprofen daily
T02 (Carprofen, N=233)	4 mg/kg of carprofen, once daily Placebo for mavacoxib days 0 and 14

Treatment was provided at any time in relation to feeding.
Detailed inclusion and exclusion criteria were specified for the study.

Efficacy endpoints: The owner recorded scores for lameness, pain and quality of life at 5 assessment point during treatment (Day 0; Days 2; within Days 5-9; within Days 12-16 and within 28-33 days after last Mavacoxib/Mavacoxib placebo treatment) and the veterinarian did similar examinations on

three occasions (Day 0, within Days 12-16 and within 28-33 days after last Mavacoxib/Mavacoxib placebo treatment).
Primary endpoint was the owner's assessment of overall improvement at the last assessment occasion (day 28-33 after last Mavacoxib/Mavacoxib placebo treatment, based on the dog's condition the last two days prior to scoring). Improvement was defined as:

- The animal is improved on at least one of the three scores and not worse on any score when compared to Day 0 assessments or:
- The animal improved on at least two of the three scores and was worse on one or none of the scores when compared to Day 0 assessments.

Discussion
This study was well conducted as regards to the use of a blinded design and the test of non-inferiority to a medical product with a documented effect for the treatment of chronic musculoskeletal pain. Furthermore, the primary evaluation was based on clinical effects 28-33 days after last Mavacoxib treatment which is relevant to the suggested dosing interval.

The inclusion criteria were relevant and ensured, by radiological as well as clinical findings, that the dogs suffered a degenerative joint disease. According to the owner´s scoring of lameness, pain and quality of life at time of enrolment, disease severity was quite equal between treatment groups.

A summary of adverse events classified as probable (A) or possible (B) within the Mavacoxib and the carprofen group respectively was provided. The digestive tract disorder cases were quite evenly spread throughout the study period and in all but one carprofen treated dog they were reported to be transient. Pre-existing conditions were also detailed for both groups. Cardiovascular disorders were more commonly pre-existing in the carprofen group, whereas endocrine and renal disorders were more common before study start in the Mavacoxib group. Generally the prevalence of pre-existing disorders was quite low and likely of no concern regarding the effect and safety evaluations.

The incidence of adverse events is quite similar in the two treatment groups. However, as previously pointed out, the occurrence of severe adverse events in the mavacoxib group is of particular concern for this long-acting substance. A study will be conducted post authorisation as part of a risk management plan agreed with CVMP, and will provide additional data on these adverse events and how to treat them in practice.

Nine per cent of dogs were withdrawn from the study. Less than two per cent were withdrawn for apparent lack of efficacy or inadequate improvement. The reasons for withdrawal for medical reasons, for the other dogs were presented, and the potential relationship to treatment discussed at the request of the CVMP. This emphasises the potential for development of serious and severe treatment related adverse events for both Mavacoxib and carprofen treated animals. However, this finding is of special concern for mavacoxib as it is exceptionally long-acting. It should be noted that these results are based on the higher dose (4 mg/kg) than now recommended in the SPC. Nevertheless, safety data presented for the new clinical field study using the recommended lower dose (2 mg/kg) does not suggest that the risk for similar events is lower than if carprofen is used.

In the study, two cases of serious adverse events likely connected to Mavacoxib treatment were reported:

- One dog had elevated levels of bilirubin and ALT at time of the screening visit. ALT was elevated at time of first treatment but bilirubin had normalised. One week after the second dose this dog had clinical signs of liver disease with elevated levels of ALT, bilirubin and AST. Plasma Mavacoxib concentration was 2.27 μg/ml at that time. The dog recovered with supportive treatment.
- Yet another Mavacoxib treated dog was withdrawn some time after the last (2^{nd}) dose with signs of duodenal ulceration and anaemia. Plasma Mavacoxib concentration was 2.54 μg/ml.

In the list of concomitant treatments, some drugs are listed that could potentially bias the efficacy assessments (e.g. corticosteroids, anaesthetic/analgesics products, tranquilisers). Information on duration and timing of this type of drugs for each study group separately was provided, and their use

in relation to the objective of this study justified. Cases that received therapeutic products that were prohibited by the protocol were recognised and documented as deviations from the study protocol. Long term use of any agent that might affect assessment of efficacy was not permitted and such cases were withdrawn from the study. The applicant has provided comprehensive lists presenting concomitant medications that might possibly have confounded efficacy assessment. A review of these tables reveals that consideration of the agents administered, along with the temporal association with efficacy assessments and the actions taken minimised any such confounding effects. The presentation of the co-medicated cases and the measures taken to avoid the introduction of bias by such treatment is acceptable to CVMP. The individual dogs suffering from different diseases prior to dosing were listed. The most commonly occurring conditions seemed to be cardiovascular and endocrine diseases and epilepsy. Some Mavacoxib treated animals were concomitantly treated with ACE inhibitors. Due to the potential risk associated with this combination in relation to renal function, the available clinical pathology data for these animals was summarised to enable a safety assessment. Current data does not indicate any risk connected to co-medication with ACE inhibitors, however the case number is to low to allow conclusions to be drawn regarding the general population. Thus, based on common knowledge regarding the potential risk for interactions between NSAIDs and ACE-inhibitors appropriate precautions for use were introduced in the SPC section 4.3.

It is not clear when in relation to feeding the treatment was administered. Since bioavailability is highly dependent on this factor information was provided on the timing of treatment in relation to feeding. The applicant explained that pharmacokinetic data demonstrating the food effect was not available before the clinical field study using a dose of 4 mg/kg was initiated. Therefore no stipulation with respect to feeding and administration times was made in the protocol for that study. Consequently it is likely that the period between feeding and dosing was variable for different cases and for different dosing occasions. The applicant has explored the effect of feeding on bioavailability and exposure through pharmacokinetic studies and PK/PD simulations. In the clinical field study evaluating efficacy and safety using the 2 mg/kg dose this knowledge has been taken into account by standardising administration to feeding and appropriate information in this regard is also reflected in the SPC.

The evaluation of effect was based primarily on the owner's assessment as calculated by per protocol, and the results were confirmed by the evaluation of the veterinarian's assessment and by calculations by ITT population. The owner's assessment corresponded well to the veterinarian's assessment and PP calculations of non-inferiority were confirmed also for the ITT population. As primary endpoint, the applicant chose to use a summary of the three different owner-assessed endpoints; musculoskeletal pain, lameness and quality of life. This "overall improvement" was defined on basis of improvement in only one or two of the three endpoints. No weighting of the three different endpoints was made. The selection of this summary score as primary endpoint was justified.

Within the last decade, an abundance of methods have been developed to assess pain and pain relief in dogs. Holton and co-workers (1998) compared three different methods (simple descriptive scale - SDS, numerical rating scale – NRS, and visual analogue scale - VAS) to assess pain in dogs (Holton et al 1998). In none of these methods was the "endpoint" weighted. To assess the efficacy of NSAIDs it is acknowledged that pain relief is the most important (and difficult) factor to measure. Thus factors closely related to pain such as lameness and quality of life, which are more easily measured, are defined and used in the assessment of effectiveness. Efforts were made to standardise the scales across the factors (normal, mild, moderate, severe, nearly incapacitated) so that all three factors provide consistent data. Sufficient justification was provided for the use of a non-weighted summary score. CVMP agreed that transformation of the ordinal scale to a binary variable (responder/non responder) has benefits when it comes to statistical evaluation. However, the proportion of responders in the new clinical study was very high and differences between the two clinical studies (4 mg/kg vs 2 mg/kg) was quite large. However, although the reason for this inter-study difference is not known, CVMP considered that the results from both studies are valid based on the chronic characteristics of the disease and the recorded non-inferiority versus the test compound.

Regarding the risk of overestimation of treatment effect it could be argued that the applicant made the definition of improved easy to attain but clearly any dog attaining improvement was receiving some benefit. With mavacoxib, improvement estimates of 79% for the all randomised set and 80% for the

per-protocol set showed there was a substantial number of dogs that did not meet the improvement criteria. The key regarding the treatment effect is that if the applicant is overestimating the effect it is done equally in the test and control groups and because improvement is not near the top of the scale and the control is well used and known to be beneficial, the test of non-inferiority can be relied on as a test of effectiveness. In effect, the three different parameters used in Owner Assessments are categorical data that cannot be merged numerically. It is therefore reasonable to propose the Owner Assessment of Overall Improvement as the primary parameter of efficacy. As is evident from the graphical representation of results, all of the individual categorical assessments "improved" in a similar manner justifying the approach used.

Determination of the efficacy and safety of mavacoxib oral tablets administered monthly at 4 mg/kg, following a loading dose interval of approximately 14 days, in the treatment of pain and inflammation associated with osteoarthritis in dogs

This field study comprises the second part of the study detailed above and includes the phase from the 5th assessment occasion (performed 25-36 days after the 2nd dose of Mavacoxib) and until 5 additional monthly doses had been administered. The study design was the same as for the previous study.

Specific for this part of the study is:
Treatment regimen: Additional to the 2 doses of Mavacoxib provided in the first part of the study, 5 monthly doses of test item were administered during this period. The first of Mavacoxib/dummy doses provided in this part of the study (Dose number 3) was administered in connection to the 5th effect assessment occasion. The following 4 doses were given in connection to the following assessment occasions (number 6 to 10). In addition, the control item (carprofen/dummy) was provided daily during the study period.
Efficacy endpoints: Effect was assessed as described in the previous study, in total 5 times within 28-33 days after each (Mavacoxib/dummy) administration.
Efficacy was assessed by the owner on each of the five assessment occasions (6-10), whereas the veterinarian did an effect assessment only at occasion number 7, 9 and 10).
Results
Compliance was better in the Mavacoxib group than in the comparator group. No efficacy data from this group had to be excluded in the per protocol analysis. Protocol deviations included marginal under/over-dosing and assessment being made outside the stipulated time range.
Efficacy:
The results for owner's assessment of overall improvement at assessment point 5 differ somewhat from what was presented in the previous study. This was due to the fact that some additional (not specified) information was available at this time of final summary of results.

Overall improvement - according to the owner's assessments - and improvement for individual parameters from 1st to 10th assessment occasion was presented for the PP population.

Safety
The list of concomitant treatments was similar as the one presented for the previous study and included some medicinal products that potentially could bias the result. The incidence of Adverse Events during the period covered in the present study was similar in the two treatment groups and of the type to be expected in a mixed population of adult dogs. Vomiting or loose faeces on a single occasion were noted in a few Trocoxil treated animals. More persistent events, including enteric conditions, were seen in very low numbers of Trocoxil treated dogs. Serious gastrointestinal events such as gastric dilatation and torsion occurred in less than one per cent of dogs.

No changes of clinical importance were noted. The only statistically significant difference seen for both treatments was an increase in red blood cell count at the 10th assessment point, and an increase in urea nitrogen and creatinine for the Mavacoxib treated animals at the 10th assessment point.

For the period covered within this study report, among the serious adverse event cases in the Mavacoxib group the applicant focussed on 5 cases which they suggest are most likely to be treatment associated:

- 14 year old dog withdrawn at assessment point 7 due to azotaemia (creatinine normal)
- 13 year old dog euthanised around assessment point 6 due to renal failure (increased BUN and creatinine). This dog underwent splenectomy previously during the study due to a splenic tumour, and its condition deteriorated soon after this.
- 11 year old dog euthanised due to renal failure (increased BUN and creatinine)
- 13 year old dog being azotaemic after study point 7 without clinical signs. At the last assessment point BUN and creatinine were increased.
- 10 year old dog withdrawn prior to assessment point 7 due to a perforating gastric ulcer. This dog was hypothyroid and suffered from cardiomyopathy at inclusion.

In only one of these dogs, Mavacoxib plasma concentrations, as measured in closest connection to adverse event occurrence, was above (7.55 µg/ml) the suggested highest limit for a safe therapeutic dose (5µg/ml).

Discussion

Efficacy

This study consists of the results from a prolongation of the previous study. According to the study protocol and data presentation, the primary efficacy endpoint was the owner's assessment of overall improvement at Assessment Point 5. The figures presented indicate that no improvement beyond assessment point 5 was noted for either the test or the control item. Furthermore, the response seems similar in both groups during the study period and no change over time is noted.

Information to support the claim for a better compliance in the test group than in the comparator group was presented. In both field efficacy and safety studies overall compliance (number of tablets administered vs. number of tablets prescribed) was 98.5% for active carprofen and 99.5% for active mavacoxib. CVMP acknowledged that the data presented indicates a similar compliance when comparing percentages but since posology differs between the two products (mavacoxib vs. carprofen), these figures hide a large difference in missed doses. However, although compliance in this sense appears considerably better for mavacoxib, it should be noted that due to the different dosing intervals (once daily for carprofen vs. once monthly for mavacoxib) the "lack of days under treatment" would be 589 days for carprofen and 7 x 30=210 days for mavacoxib. Thus, the presentation of difference in missed doses (589 for carprofen vs 7 for mavacoxib) exaggerates the benefit of mavacoxib to some extent. Yet another aspect connected to compliance is how to handle the situation where the owner is uncertain whether he/she as given the medicine or not. Furthermore, the appropriateness of long acting-treatment of chronic musculoskeletal disease could be questioned due to the fact that such conditions often manifest in a cyclic pattern and treatment should be adjusted in close coherence to the clinical signs to avoid unnecessary treatment. All those aspects have been thoroughly discussed and assessed and although the claimed increase of compliance with Trocoxil as compared to other NSAIDs could be questioned, CVMP accepted increased compliance as an additional benefit for Trocoxil as the long effect duration for mavacoxib will ensure continuous exposure and in case of problems with dosing, Trocoxil could be administered by a professional whereas this would not be practical for an NSAID with once or twice daily dosing.

Safety

The safety presentation consists mainly of general statements, and the provision of data lists of dogs having experienced adverse events. Six cases of serious treatment related adverse events are presented in slightly more detail. These cases point at the risk for development of potentially severe renal and gastrointestinal disorders. These cases are of particular concern in light of the slow elimination time for Mavacoxib. Since the patients with a prolonged elimination period cannot be identified, a treatment period exceeding that recommended in the SPC should not be accepted in any dog. The recommended 6.5 month treatment period was justified to CVMP. Within the 4 mg/kg field efficacy and safety study, mavacoxib was administered for a total of seven times. Assuming an average dosing interval of 30 days plus an additional 15 days between first and second administration ("jump start") assessment point 10 occurred on study day 195 (6.5 months). Note; daily carprofen administration was terminated at AP 10. Thus animals enrolled onto study were treated safely for up to 6.5 months. CVMP considers that a treatment (and observation) period of 6.5 months justifies the recommended treatment period proposed on the SPC.

As noted some medicinal product which may have biased the efficacy assessments (e.g. corticosteroids, anaesthetic/analgesic products, tranquilisers), were used during the study. Additional information on duration and timing of this type of drug treatment was provided.

The clinical pathology data was summarised, for the two treatment groups and for the different sampling occasion. Mean and range or SD, and outliers as compared to an appropriate reference range were presented, and a comparison to baseline levels made. In addition, summary data were presented from all haematological and clinical chemistry parameters specified in the Study Protocol at the request of the CVMP. The most important clinical pathology findings were highlighted within the final study report for the 4 mg/kg field safety and efficacy study. Due to the bulk of the data it was considered that it was not reasonable to insert the complete summary and analyses of all laboratory data into the report. CVMP acknowledges that significant findings were highlighted in the study report, and according to the "Data Summary and Analysis" no other relevant deviances were apparently noted.

Measurement of residual Mavacoxib plasma concentrations in Mavacoxib-treated dogs enrolled in the field study

In this GCP study, conducted in 2006, blood samples were collected from Mavacoxib treated dogs, included in the field studies for clinical pathology and Mavacoxib quantification. For this purpose one single sample was collected at different intervals after Mavacoxib treatment was ended.

145 of the Mavacoxib treated dogs included in the field studies aged from 2-15 years, weight 5.7-55.5 kg were included in the study. The dogs did not receive Mavacoxib from the end of the field study until blood sampling. Mavacoxib quantifications were used to perform population pharmacokinetics and the results from these analyses are presented in the Pharmacokinetic section. 46.2 % of the dogs were treated with anti-inflammatory medication at time of sampling.

This study aims to provide information on potential long term effects of Mavacoxib treatment. It was not clear how animals were selected for this study. The applicant was asked to justify why not all animals previously treated with Mavacoxib within the field studies, were included in the present follow-up study. The applicant confirmed that when the first data indicating an extended half life in osteoarthritic animals became available, it was decided to collect follow-on samples to further characterise mavacoxib's pharmacokinetic behaviour. However, not all patient owners were able or chose to participate in the follow on study.

The suggested claim for anti-inflammatory effect was justified. The applicant argues that most of the studies for dose selection in the dossier focus on exploring lameness and pain in models of pain and inflammation – i.e., the synovitis model, the carrageenan model of pain and inflammation and the osteoarthritis model, all models associated with causing pain by causing inflammation. Thus, support for the anti-inflammatory effect is claimed from all these studies and mavacoxib, like any COX1/COX2 inhibiting non-steroidal anti-inflammatory drugs in general, exhibit their analgesic effect predominately via their anti-inflammatory effect. The connection between the analgesic and anti-inflammatory effect for NSAIDs is accepted and CVMP acknowledged that these effects can hardly be separated and evaluated apart from each other. To conclude, sufficient support for an anti-inflammatory claim has been presented.

Conclusion on the Field Studies

A single field study was initially submitted to demonstrate efficacy and safety in the clinical situation. The applicant has chosen to present data in three different reports covering different parts of the study period. During the whole study period the animals were treated with 7 doses of Mavacoxib in accordance with the suggested posology. The field study was well conducted as regards to the use of a blinded design and the test of non-inferiority to a medical product (carprofen) with a documented effect for the treatment of chronic musculoskeletal pain, provided according to approved recommendations (4 mg/kg, once daily). The study included 474 dogs. The primary efficacy evaluation was based on clinical effects 28-33 days after the previous Mavacoxib treatment which is

relevant in relation to the suggested dosing interval. Primary endpoint was the owner's assessment of overall improvement according to a summary score, as determined one month after the second Mavacoxib dose which constituted the time where a plateau effect was reached. The owner-based assessment was supported by a similar assessment performed by the veterinarian. The inclusion criteria seem relevant and ensured, by radiological as well as clinical observations, that the dogs suffered a degenerative joint disease. A similar panorama of disorders was noted in both treatment groups and baseline assessment of disease severity was also similar in the two groups. The results demonstrated a similar and continuous improvement ranging from around 45 % at Day 2 after treatment, to about 70 % at Day 25-36 after the second Mavacoxib dose. At this later time point, non-inferiority was demonstrated: a 90% confidence interval for treatment difference was –2.6 % for the per-protocol analysis (90% confidence interval from –9.1% to +3.9%). Safety assessment showed a quite low and similar incidence of adverse events in both groups. Gastrointestinal disturbances were the predominating event noted and were seen in 8.6 % of the Mavacoxib treated animals and in 7.7 % of the Carprofen treated animals.

To support the proposed dose 2 mg/kg BW, the applicant presented results from a new clinical efficacy and safety study including 124 clinical cases suffering osteoarthrosis. The results from this study demonstrate that the effect of mavacoxib at the proposed dose (2 mg/kg) is non-inferior to the effect of carprofen. In this study the tolerance pattern was similar in the two treatment groups. Gastrointestinal disorders were quite commonly noted in both groups, renal affection was also noted in a few animals in both groups. In the mavacoxib group, one dog died from a septicaemic condition including duodenal and gastric ulceration. In the carprofen group, two dogs died from gastrointestinal ulceration.

In the initially submitted field study non-inferiority to carprofen treatment was demonstrated at the dose level 4 mg/kg. Support for effect regarding the suggested dose of 2 mg/kg is provided through the results of the new clinical field study. For both clinical field studies the safety data indicates that for some dogs mavacoxib treatment is connected to an increase in clinical chemistry parameters reflecting renal integrity. The occurrence of adverse events is mainly connected to gastrointestinal disturbances and to low extent, renal disturbances. Some cases of a potentially life threatening character occurred in both clinical studies, which is of concern due to the fact that the long elimination half-life of the active substance precludes an immediate termination of treatment. The reduction of the mavacoxib dose from 4 mg/kg to 2 mg/kg did not seem to improve the tolerance pattern as compared to carprofen. However, as documented in the dossier, the incidence of adverse reactions was not higher in Troxocil treated animals as compared to the daily administered NSAID used as a positive control in the studies. Acknowledging the fact that the prolonged exposure following mavacoxib might represent an additional risk as treatment/exposure discontinuation is not feasible, CVMP regarded this additional risk as acceptable knowing that long term treatment with NSAIDs is common and in most cases without signs of adverse reactions. This possible increased risk will be further monitored as part of a large additional post-approval clinical safety study. The results from this study will be presented as described in a risk management plan agreed with CVMP and the appropriate use of Trocoxil will be further discussed following the results from this study.

Mavacoxib is an NSAID with the typical safety characteristics of this therapeutic class, which requires a close monitoring of treatment outcome and a preparedness to adjust dose, or to immediately terminate treatment, in case of unacceptable adverse events. Side effects may be fatal and there is a special concern related to the use of NSAIDs in case of surgery and emergency care. At the proposed dose (2 mg/kg) the safety profile of mavacoxib seems similar to the well known comparator carprofen but the typically long elimination time for mavacoxib hampers any swift dose adjustment or treatment termination. In practice, this means that treatment cannot be terminated should adverse effects occur, acute surgery be needed or in case of lack of efficacy where it would be needed to switch to other treatment. The agreement to include an additional post authorisation study in a risk management plan agreed by CVMP will provide additional data on the use of Trocoxil in practice with a large number of dogs and closely monitor all adverse events and their treatment. Based on the results of this study there may be a need to amend the SPC warnings at a later stage based on experience.

5. BENEFIT-RISK BALANCE

Benefit:
The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

The applicant has demonstrated by a non-inferiority study that the anticipated effects of mavacoxib treatment are similar to those of the comparator product containing carprofen.

The dose has been selected to provide optimum treatment benefits.

Additional benefits connected to Trocoxil treatment include better compliance as compared to other NSAIDS, due to the once monthly dosing strategy.

The product is safe for the user, and for the environment, when used as recommended.

Suitable warnings and precautions are indicated in the SPC.

Risk:
The safety profile of Mavacoxib seems to be quite similar to other products in the NSAID class and is mainly characterised by the risk for gastrointestinal and likely also renal disturbances which could potentially be life-threatening. The extremely long elimination half life (about 40 days on average) for Mavacoxib constitutes a specific and significant risk factor for this product as it precludes any prompt dose adjustment, or the termination of treatment in case of treatment related adverse events.

The fact that dosing can not immediately be adjusted or terminated for this potential patient group constitutes a specific concern. The applicant has agreed to a risk management plan, as part of which they will conduct a study, post authorisation and prior to marketing, which will look in detail at the severity and duration of adverse reactions after treatment with Trocoxil. The results from this study are to be presented according to a risk management plan.

Conclusion
The overall risk benefit analysis for Trocoxil is deemed positive with a sufficiently clear and complete SPC and product literature. However, as there may be an additional risk related to the prolonged exposure to mavacoxib following treatment, the benefit/risk balance will be re-evaluated pending the outcome of the postmarketing clinical safety study.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Trocoxil were considered to be in accordance with the requirements of Council Directive 2001/82/EC.